9-17-07

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ATTORNEY DOCKET NO. 10031165-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): John Link et al.

Serial No.: 10/804,938 **Examiner:** Robert Thomas Crow

Filing Date: March 19, 2004 **Group Art Unit:** 1634

Title: DEVICES AND METHODS FOR ISOLATING RNA

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on July 25, 2007

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☐ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

☐	one month	$ 120.00
☐	two months	$ 450.00
☐	three months	$1020.00
☐	four months	$1590.00

☐ The extension fee has already been filled in this application.

☒ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $500.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078** pursuant to 37 CFR 1.25.

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Respectfully submitted,

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VIA EXPRESS MAIL EV 955 153 836 US

APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/804,938
	Confirmation Number	8132
	Attorney Docket No.	10031165-1
	Filing Date	March 19, 2004
	First Named Inventor	Link, John
	Examiner	CROW,ROBERT
	Group Art	1634
	Title: Devices and Methods for Isolating RNA	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated March 26, 2007 and June 26, 2007. No claims have been allowed. Claims 1, 3-15, 20 and 21 are pending and appealed herein. A Notice of Appeal was filed on July 25, 2007.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-1078, reference no. 10031165-1 to cover the fee required under 37 C.F.R. §1.17(b) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-1078, reference no. 10031165-1.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Agilent Technologies, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on March 19, 2004 with Claims 1-19. During the course of prosecution, Claims 16-19 were withdrawn, Claim 2 was cancelled and Claims 20 and 21 were added by amendment. Accordingly, Claims 1, 3-15, 20 and 21 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

Amendments to Claims 1, 3, 4 and 5 were filed subsequent to issuance of the Final Rejection. In the Advisory Action dated June 26, 2007, the Examiner indicated that these amendments would be entered for purposes of appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

The appealed claims are drawn to a method of preparing a complementary RNA (cRNA) sample substantially free of contaminants.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 1 claims a method of preparing a cRNA sample substantially free of contaminants, comprising the following steps:

(a) preparing a cRNA sample;

(b) adding an organic solvent to said preparation of (a);

(c) contacting a cRNA isolation column with the organic preparation of step (b),

wherein said cRNA isolation column comprises a membrane selected from the group consisting of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof;

(d) adding to a preparation of step (c) one or more DNase enzymes;

(e) adding to a preparation of step (d) a wash buffer comprising a chaotropic salt; and

(f) eluting said cRNA in a purified form from said column of step (c)

(see specification at page 5, lines 19-21; page 21, lines 10-23; page 22, lines 18-27; and original Claim 1).

Claim 3 claims the method of Claim 1, wherein said membrane is a polysulfone and polyvinylpyrrolidone membrane (see specification at page 21, lines 10-23).

Claim 4 claims the method of Claim 3, wherein said polysulfone and polyvinylpyrrolidone membrane is an asymmetric membrane comprised of polysulfone PVP (see specification at page 21, lines 10-23).

Claim 5 claims the method of Claim 3, wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 0.4 μm to about 0.6 μm on a lower side (see specification at page 21, lines 10-23; page 45, lines 6-8; and original Claim 5).

Claim 6 claims the method of Claim 5, wherein said membrane has a pore size of about 0.4 μm on said lower side (see specification at page 45, lines 6-8 and original Claim 6).

Claim 7 claims the method of Claim 1, wherein said cRNA is labeled (see specification at page 20, line 29 - page 21 line 2; and original Claim 7).

Claim 8 claims the method of claim 7, wherein said label is either radioactive or fluorescent (see specification at page 20, line 29 - page 21 line 2; and original Claim 8).

Claim 9 claims the method of claim 8, wherein said fluorescent label is a cyanine dye (see specification at page 20, line 29 - page 21 line 2; and original Claim 9).

Claim 10 claims the method of Claim 1, wherein said purified cRNA is from about 55% to about 65% pure (see specification at page 21, lines 3-9).

Claim 11 claims the method of Claim 1, wherein said purified cRNA is from about

65% to about 75% pure (see specification at page 21, lines 3-9).

Claim 12 claims the method of Claim 1, wherein said purified cRNA is from about 75% to about 85% pure (see specification at page 21, lines 3-9).

Claim 13 claims the method of Claim 1, wherein said purified cRNA is from about 85% to about 95% or greater pure (see specification at page 21, lines 3-9).

Claim 14 claims the method of Claim 1, wherein said organic solvent is ethanol (see specification at page 11, lines 10-13).

Claim 15 claims the method of Claim 1, wherein said isolation column is either a SiCw column or an RNA isolation column (see specification at page 5, lines 22-30; and original Claim 15).

Claim 20 claims the method of Claim 1, wherein said one or more DNase enzymes is selected from the group consisting of DNase 1, DNase II, and a combination thereof (see specification at page 12, lines 14-17).

Claim 21 claims the method of claim 1, wherein said chaotropic salt is selected from the group consisting of guanidine isothiocyanate, ammonium isothiocyanate, guanidine hydrochloride, and a combination thereof (see specification at page 12, lines 24-32).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

As best understood by the Appellants, the current grounds of rejection are as follows:

I. Claims 3-6 stand rejected as being indefinite under 35 U.S.C. § 112, second paragraph.

II. Claims 1, 3-6, 10-15, and 20-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, NY, pp. 7.12-7.15 and pp. 7.23-7.29 (1989) ("Sambrook") in view of Wang et al. (U.S. Patent No. 5,219,727) ("Wang et al. '727") and further in view of Wang et al. (U.S. Patent No. 5,906,742) ("Wang et al. '742") as evidenced by Pall Life Sciences (Bulletin #FAM-1050-C, Pall Corporation, Filterite Advanced Materials Division, San Diego, CA, 2002) ("Pall Life Sciences").

III. Claims 7-9 stand rejected as being unpatentable over Sambrook in view of Wang et al. '727 and Wang et al. '742 as evidenced by Pall Life Sciences and further in view of Waggoner (U.S. Patent No. 5,627,027) ("Waggoner").

ARGUMENT

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 1, 3-4, 7-9, 14-15, and 20-21 drawn to a method of preparing a cRNA sample substantially free of contaminants, comprising the following steps: (a) preparing a cRNA sample; (b) adding an organic solvent to said preparation of (a); (c) contacting a cRNA isolation column with the organic preparation of step (b), wherein said cRNA isolation column comprises a membrane selected from the group consisting of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof; (d) adding to a preparation of step (c) one or more DNase enzymes; (e) adding to a preparation of step (d) a wash buffer comprising a chaotropic salt; and (f) eluting said cRNA in a purified form from said column of step (c);

Group II: Claim 5, drawn to the method of Claim 3, wherein the polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size

ranging from about 0.4 μm to about 0.6 μm on a lower side;

Group III: Claim 6, drawn to the method of Claim 5, wherein said membrane has a pore size of about 0.4 μm on said lower side;

Group IV: Claim 10, drawn to the method of Claim 1, wherein the purified cRNA is from about 55% to about 65% pure;

Group V: Claim 11, drawn to the method of Claim 1, wherein the purified cRNA is from about 65% to about 75% pure;

Group VI: Claim 12, drawn to the method of Claim 1, wherein the purified cRNA is from about 75% to about 85% pure; and

Group VII: Claim 13, drawn the method of Claim 1, wherein the purified cRNA is from about 85% to about 95% or greater pure.

Claims 3-6 are not indefinite under 35 U.S.C. § 112, second paragraph.

Group I: Claims 3-4

In the Final Office Action dated March 26, 2007, Claims 2-6 were rejected as indefinite under 35 U.S.C. § 112, second paragraph, based on the recitation in claims 2-5 of the terms "BTS" and/or "MMM". The Examiner stated that these terms are acronyms, the meanings of which may change over time, and suggested that each of the claims be amended to recite each of the polymers in each instance by their respective full names.

Claim 2 was cancelled in the Amendment and Response filed on May 25, 2007, and Claims 3-5 were amended as suggested by the Examiner. Based on the Examiner's entry of the proposed amendments and the Examiner's failure to address the 35 U.S.C. § 112, second paragraph, rejection in the Advisory Action dated June 26, 2007, the Appellants submit that the rejection of Claims 3-4 under 35 U.S.C. § 112, second paragraph, has been adequately addressed.

Group II: Claim 5

Without repeating the argument above, the Appellants submit that, based on the amendments entered by the Examiner, the rejection of Claim 5 under 35 U.S.C. § 112, second paragraph, is moot.

Group III: Claim 6

Without repeating the argument above, the Appellants submit that, based on the amendments entered by the Examiner, and the dependency of Claim 6 from Claim 5, the rejection of Claim 6 under 35 U.S.C. § 112, second paragraph, is moot.

In view of the arguments above, the Appellants submit that claims 3-6 are not indefinite under 35 U.S.C. §112, second paragraph, and respectfully request reversal of this rejection.

Claims 1, 3-6, 10-15, and 20-21 are not obvious under 35 U.S.C. § 103(a) over Sambrook in view of Wang et al. '727, and further in view of the Wang et al. '742 as evidenced by Pall Life Sciences.

Group I: Claims 1, 3-4, 7-9, 14-15, and 20-21

As noted above, the claims of this Group are drawn to a method of preparing a cRNA sample substantially free of contaminants, comprising the following steps: (a) preparing a cRNA sample; (b) adding an organic solvent to said preparation of (a); (c) contacting a cRNA isolation column with the organic preparation of step (b), wherein said cRNA isolation column comprises a membrane selected from the group consisting

of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof; (d) adding to a preparation of step (c) one or more DNase enzymes; (e) adding to a preparation of step (d) a wash buffer comprising a chaotropic salt; and (f) eluting said cRNA in a purified form from said column of step (c).

As best understood by the Appellants, the Examiner asserts that the combination of Sambrook, Wang et al. '727 and Wang et al. '742 teaches or suggests each and every element of Claims 1, 3-6, 10-15, and 20-21. The Examiner acknowledges that Sambrook and Wang et al. '727 are deficient in that they each fail to teach or suggest MMM (polysulfone and polyvinyl pyrrolidone) membranes (Final Rejection, page 6). The Examiner, therefore, relies upon Wang et al. '742 to remedy the deficiencies of Sambrook and Wang et al. '727. According to the Examiner, it would have been obvious to modify the method comprising a membrane as taught by Sambrook and Wang et al. '727 with the membrane as taught by Wang et al. '742 with a reasonable expectation of success.

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. *In re Royka*, 180 U.S.P.Q. 580 (CCPA 1974). *See Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342 (Fed. Cir. 2007); 83 U.S.P.Q.2D (BNA) 1289 ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); *and see KSR Int'l Co.* at 1741("a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art"); *and see Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006); 80 U.S.P.Q.2D (BNA) 1641 ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches,

whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,' (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004); 73 U.S.P.Q.2D (BNA) 1141)).

It is respectfully submitted that the Examiner's *prima facie* case of obviousness is deficient because the combined teachings of Sambrook, Wang et al. '727 and Wang et al. '742 fail to teach or suggest each and every element of the claimed invention. Specifically, the combined references fail to teach or suggest a cRNA purification method in which the cRNA isolation column comprises a membrane that does not have an active binding agent associated therewith. As indicated above, the instant claims are directed to a method wherein the "cRNA isolation column comprises a membrane selected from the group consisting of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof." The use of the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim phrase. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931). Because the listed membranes are passive separation membranes, the closed claim language excludes membranes that have an active binding agent associated therewith. Furthermore, the proposed combination fails to teach or suggest a membrane which passively retains an RNA precipitate.

Sambrook is directed to a method of purifying poly $(A)^+$ RNA using an oligo(dT) cellulose column in a Dispocolumn (BioRad) (or a pasture pipette, plugged with sterile glass wool). RNA is dissolved in sterile water, and the solution is heated to 65°C. Sambrook indicates that heating the RNA disrupts regions of secondary structure that might involve the poly (A) tail. The solution is then cooled to room temperature and applied to the column in an equal amount of column loading buffer. The column is washed and then eluted from the oligo(dT) cellulose using sterile, RNAase-free elution buffer. The material obtained after a single round of chromatography on oligo(dT)-cellulose usually contains approximately equal quantities of polyadenylated and non-polyadenylated species of RNA. (See Sambrook, pages 7.26 and 7.27).

The Examiner interprets the glass wool plug of Sambrook to be a "membrane" as that term is used in the instant claims. According to the Examiner, "a cursory review of the specification yields no limiting definition of a 'membrane,' other than that the membrane performs a passive role by acting as a physical barrier to a precipitate" (Advisory Action dated 6/26/07, page 2). The Examiner then concludes that because the glass wool forms a physical barrier, it constitutes a membrane as that term is used in the instant specification.

The Appellants disagree with the Examiner's conclusion that the glass wool plug constitutes a membrane as that term is used in the context of the instant claims. The membranes utilized in the presently claimed method are described as follows in the instant specification.

> **[0072]** The mechanism of RNA isolation is via precipitation. RNA, either in a purified or semi-purified (following prefiltration) form or in a complex biological sample, will precipitate in the presence of guanidine and ethanol. This precipitate can be collected via, for example, centrifugation. The RNA isolation membrane column of the present invention facilitates the collection of the RNA precipitate, washing of the collected precipitate (reduced wash volumes and centrifugation times) and re-suspension and elution of the target nucleic acid.
>
> **[0073]** Although the membrane material plays a passive role, acting as a physical barrier to the precipitate, the nature of the polymeric material is important for efficient precipitate collection and to reduce absorptive losses. For example, comparison of various pore sizes of membranes results in changes in the mass recovery of RNA. Similarly, comparison of membranes prepared from different polymeric constituents also varies the mass recovery of RNA.

Specification as filed, page 19, line 23 to page 20, line 6; and Published Application, page 7.

It is clear from the closed claim language of independent Claim 1 and the above description that the membranes of the instant claims are not associated with an active binding agent and therefore the membranes play a passive role, acting as physical barriers to the RNA precipitate.

In contrast, the glass wool of the Sambrook method is associated with oligo-(dT)-cellulose (pg 7.26, section 2) which actively binds poly(A)$^+$ RNA. The mechanism of separation and purification described by Sambrook is based on the affinity binding of the poly(A)$^+$ RNA to the oligo(dT)-cellulose by virtue of specific Watson-Crick base pairing. There is no teaching or suggestion that the glass wool passively retains an RNA precipitate for purification. Rather, the glass wool is associated with packed oligo-(dT)-cellulose, and it is the oligo-(dT)-cellulose that actively binds the poly(A)$^+$ RNA. In fact, Appellants find no mention anywhere in the column purification method described by Sambrook of an RNA precipitate being retained on a column.

In an attempt to establish a *prima facie* case of obviousness, the Examiner asserts that it would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising a membrane as taught by Sambrook and Wang et al. '727 with the membranes as taught by Wang et al. '742 with a reasonable expectation of success. According to the Examiner:

> The modification would result in the use of the asymmetric microfiltration membrane of Wang et al. '742 in place of the glass wool membrane of Sambrook et al. The ordinary artisan would have been motivated to make such a modification because such a modification would have resulted [in] a method of preparing a cRNA sample substantially free of contaminants having the added advantage of allowing the quick detection of components contained in liquid samples as explicitly taught by Wang et al ['742].

Advisory Action dated 6/26/07, page 2.

The deficiencies of Sambrook with respect to the instant claims are described above. The Examiner's proposed combination of Wang et al. '727 and Wang et al. '742 with Sambrook fails to cure the deficiencies of Sambrook. The Examiner relies on Wang et al. '727 merely for its disclosure of cRNA preparation (Final Office Action dated March 26, 2007, page 4, last paragraph to page 5, line 3). The Appellants have not found, and the Examiner has failed to identify, any teaching or suggestion in Wang et al. '727 of a cRNA purification method in which the method utilizes a membrane column in which the membrane is not associated with an active binding agent or in which the membrane passively retains an RNA precipitate. As such, the addition of the Wang et al. '727 reference fails to cure the deficiencies of Sambrook.

The addition of the Wang et al. '742 reference also fails to cure the deficiencies of Sambrook. The substitution of the asymmetric microfiltration membrane of Wang et al. '742 for the glass wool of Sambrook would result in a method wherein the asymmetric microfiltration membrane of Wang et al. '742 is associated with the oligo(dT)-cellulose described by Sambrook. As such, the substitution would result in a method wherein the membrane is associated with an active binding agent. Furthermore, the proposed combination would not teach or suggest a membrane which passively retains an RNA precipitate because Sambrook does not disclose RNA in a precipitate form on the column.

Wang et al. '742 indicates that the asymmetric microfiltration membranes described therein may be used to separate solids from a solid-containing liquid, providing as an example the separation of blood cells from plasma (Abstract and column 5, lines 35-39). However, The Appellants have not found, and the Examiner has failed to identify, any teaching or suggestion in Wang et al. '742 of a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains an RNA precipitate. As such, the addition of Wang et al. '742 fails to cure the combined deficiencies of Sambrook and Wang et al. '727.

In the Advisory Action dated June 26, 2007, the Examiner cites *In re Kerkhoven*,

626 F. 2d 846, 850; 205 U.S.P.Q. 1069, 1072 (CCPA 1980), for the proposition that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose." The Examiner asserts that the modification of replacing the glass wool of Sambrook with the asymmetric microfiltration membrane of Wang et al. '742 represents a combination of equivalents known for the same purpose.

The Appellants submit that *In re Kerkhoven* is inapplicable to the combination of references proposed by the Examiner. As explicitly stated by the Examiner "the replacement of the asymmetric microfiltration membrane materials for (rather than [in] addition to) the glass wool membrane would have resulted [in] a method of preparing a cRNA sample substantially free of contaminants . . . " (Advisory Action, page 2, last line to page 3, line 3). Thus, the proposed combination of references is not a "combination of two compositions," but rather a proposed replacement of one composition for another. As such, the holding of *In re Kerkhoven* is inapplicable.

In view of the above, the Appellants contend that a *prima facie* case of obviousness has not been established because the recited combination of references fails to teach or suggest all the elements of the rejected claims, namely a cRNA purification method in which the method utilizes a membrane "from the group consisting of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof," i.e., a membrane that passively retains a cRNA precipitate. As such, Appellants respectfully request reversal of the rejection.

Group II: Claim 5

Claim 5 is drawn to the method of Claim 3 and further specifies that the polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 0.4 μm to about 0.6 μm on a lower side.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest a cRNA purification method, wherein the polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 0.4 μm to about 0.6 μm on a lower side.

In the Final Office Action of March 26, 2007, the Examiner asserts that Wang et al. '742 teaches that the MMM membrane has a pore size ranging from about 30μm to about 40μm on an upper side and a pore size of about 0.8μm on a lower side. In support of this assertion, the Examiner relies on column 10, line 59 – column 11, line 1, of Wang et al. '742 which indicates that the membrane demonstrates an "isotopic region including pore sizes around 1.0μm . . . followed by an asymmetric region that opens from pore sizes of approximately 2.0μm to about 50μm from the end of the isotropic region to the case surface." The Examiner further asserts that:

> **In addition, the courts have stated where the claimed ranges "overlap or lie inside the ranged disclosed by the prior art" and even when the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists (see *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner*, 778 F2d 775. 227 USPQ 773 (Fed. Cir. 1985).**

Final Office Action, page 6, last paragraph.

As an initial matter, the Appellants note that Claim 5 does not recite "wherein said MMM membrane has a pore size of about 0.8 μm on a lower side" as indicated by the Examiner on page 7, lines 1-4, of the Final Office Action dated March 26, 2007. Rather, Claim 5 recites "wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 0.4 μm to about 0.6 μm on a lower side." As such, the pores on the lower side of the membrane of Claim 5 are approximately one half the size of the pores on the lower side of the membrane described by Wang et al. '742.

Appellants therefore submit that since Wang et al. '742 does not teach or suggest a pore size range on the lower side of the membrane from about 0.4 μm to about 0.6 μm, and since the remaining cited references are silent with respect to membrane pore size, the proposed combination of references fails to teach this element, and a prima facie case of obviousness has therefore not been established.

The Examiner cites *In re Wertheim* for the proposition that "even when the claimed ranges and the prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists" (Final Office Action dated March 26, 2007, page 6, last paragraph).

Appellants submit that even if the disclosure provided by Wang et al. '742, in combination with the other cited references, was sufficient to establish a *prima facie* case of obviousness, the Appellants have provided sufficient evidence in the instant specification to rebut such a *prima facie* case.

Specifically, the Appellants have demonstrated unexpected results for cRNA purifications conducted using membranes with the claimed pore size ranges.

For example, Figure 14 shows five different columns used to purify cRNA, (a) 0.1 μm MMM, (b) 0.4 μm MMM, (c) 0.6 μm MMM and (d) 0.8 μm MMM, wherein the pore sizes refer to the pore sizes on the bottom surface of the membrane of the claimed method (Specification, page 45, lines 6-19). Results from these experiments suggest that greater cRNA yield can be obtained using membranes with pore sizes within the claimed range as compared with membranes with pore sizes outside of the claimed range. As such, Appellants submit that sufficient evidence has been provided to rebut a *prima facie* case of obviousness which relies on the 1.0 μm pore size described by Wang et al. '742.

In view of the above, Appellants respectfully request reversal of the rejection.

Group III: Claim 6

Claim 6 is drawn to the method of Claim 5, wherein said membrane has a pore size of about 0.4 μm on said lower side.

Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest a cRNA purification method, wherein the polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said membrane has a pore size of about 0.4 μm on the lower side. The membrane of Claim 6 has a pore size on the lower side of the membrane which is approximately 2.5 fold smaller than the smallest pore size described by Wang et al. '742. As such, Appellants submit that Wang et al. '742 fails to teach or suggest a membrane, wherein the membrane has a pore size on the lower side of the membrane of about 0.4 μm as presently claimed. Since the remaining cited references are silent with respect to membrane pore size, the proposed combination of references fails to teach this element, and a prima facie case of obviousness has therefore not been established. As such, Appellants respectfully request reversal of the rejection.

Group IV: Claim 10

Claim 10 is drawn to the method of Claim 1, wherein the purified cRNA is from about 55% to about 65% pure.

The application of the combined cited references to Claim 1 has been discussed previously herein. Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a

cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest purified cRNA, wherein the purified cRNA is from about 55% to about 65% pure.

In the Final Office Action, the Examiner stated that "[b]ecause Sambrook et al teach the RNA is separated and purified (page 7.15, paragraph ii), the RNA of Sambrook et al is encompassed by the broadly claimed purity of instant claims 10 – 13" (Final Office Action dated March 26, 2007, page 4, lines 14-16). The Appellants contend that the Examiner's conclusion is flawed because it fails to take into account the teachings of the Sambrook reference as a whole. In an attempt to establish this rejection, the Examiner relies on page 7.15, paragraph ii, of Sambrook, which recites "[i]f desired, poly(A)$^+$RNA can be purified from the preparation of total cytoplasmic RNA and freed from contaminating oligodeoxyribonucleotides by chromatography on oligo(dT)-cellulose (see pages 7.26-7.29)."

As indicated, the purification of poly(A)$^+$RNA is described on pages 7.26 to 7.29 of Sambrook. On page 7.27, Sambrook discusses the purity of the poly(A)$^+$RNA obtained using the disclosed column purification method.

> The material obtained after a single round of chromatography on oligo(dT)-cellulose usually contains approximately equal quantities of polyadenylated and non-polyadenylated species of RNA. To purify poly(A)$^+$RNA further, heat the RNA to 65°C for 3 minutes and then cool it quickly to room temperature. Adjust the concentration of NaCL in the eluted RNA to 0.5M, and carry out a second round of chromatography on the same column of oligo(dT)-cellulose.

Sambrook, page 7.27, last paragraph.

The above paragraph indicates that the material obtained using the disclosed column purification method contains approximately equal quantities of polyadenylated and non-polyadenylated species of RNA, i.e., the poly(A)$^+$RNA product is only approximately 50% pure.

Appellants contend that because the poly(A)$^+$RNA product described by Sambrook is only approximately 50% pure, Sambrook fails to teach or suggest the claimed method, wherein the purified cRNA is from about 55% to about 65% pure. The Appellants have not found, and the Examiner has not cited, any language in either Wang et al. '727 or Wang et al. '742 which discusses purity levels of cRNA. As such, the combination of Sambrook, Wang et al. '727 and Wang et al. '742 also fails to teach or suggest the claimed method, wherein the purified cRNA is from about 55% to about 65% pure.

Since the proposed combination of references fails to teach or suggest each and every element of the instant claims, Appellants submit that a *prima facie* case of obviousness has not been established and respectfully request reversal of the rejection.

Group V: Claim 11

Claim 11 is drawn to the method of Claim 1, wherein the purified cRNA is from about 65% to about 75% pure.

The application of the combined cited references to Claim 1 has been discussed previously herein. Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest purified cRNA, wherein the purified

cRNA is from about 65% to about 75% pure.

As discussed above with respect to Group IV, Claim 10, the poly(A)$^+$RNA product obtained using the Sambrook column purification method is only approximately 50% pure. As such, the arguments presented above with respect to Claim 10 apply *a fortiori* to Claim 11 which recites a higher level of purity than Claim 10.

The Appellants have not found, and the Examiner has not cited, any language in either Wang et al. '727 or Wang et al. '742 which discusses purity levels of cRNA. As such, the combination of Sambrook, Wang et al. '727 and Wang et al. '742 also fails to teach or suggest the claimed method, wherein the purified cRNA is from about 65% to about 75% pure.

Since the proposed combination of references fails to teach or suggest each and every element of the instant claims, Appellants submit that a *prima facie* case of obviousness has not been established and respectfully request reversal of the rejection.

Group VI: Claim 12

Claim 12 is drawn to the method of Claim 1, wherein the purified cRNA is from about 75% to about 85% pure.

The application of the combined cited references to Claim 1 has been discussed previously herein. Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest purified cRNA, wherein the purified cRNA is from about 75% to about 85% pure.

As discussed above with respect to Group IV, Claim 10, the poly(A)$^+$RNA product obtained using the Sambrook column purification method is only approximately 50% pure. As such, the arguments presented above with respect to Claim 10 apply *a fortiori* to Claim 12 which recites a higher level of purity than Claim 10.

The Appellants have not found, and the Examiner has not cited, any language in either Wang et al. '727 or Wang et al. '742 which discusses purity levels of cRNA. As such, the combination of Sambrook, Wang et al. '727 and Wang et al. '742 also fails to teach or suggest the claimed method, wherein the purified cRNA is from about 75% to about 85% pure.

Since the proposed combination of references fails to teach or suggest each and every element of the instant claims, Appellants submit that a *prima facie* case of obviousness has not been established and respectfully request reversal of the rejection.

Group VII: Claim 13

Claim 13 is drawn to the method of Claim 1, wherein the purified cRNA is from about 85% to about 95% or greater pure.

The application of the combined cited references to Claim 1 has been discussed. Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a cRNA purification method in which the method utilizes a membrane column in which the membrane is not associated with an active binding agent or in which the membrane passively retains a cRNA precipitate.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach or suggest purified cRNA, wherein the purified cRNA is from about 85% to about 95% or greater pure.

As discussed above with respect to Group IV, Claim 10, the poly(A)$^+$RNA product obtained using the Sambrook column purification method is only approximately 50%

pure. As such, the arguments presented above with respect to Claim 10 apply *a fortiori* to Claim 13 which recites a higher level of purity than Claim 10.

The Appellants have not found, and the Examiner has not cited, any language in either Wang et al. '727 or Wang et al. '742 which discusses purity levels of cRNA. As such, the combination of Sambrook, Wang et al. '727 and Wang et al. '742 also fails to teach or suggest the claimed method, wherein the purified cRNA is from about 85% to about 95% or greater pure.

Since the proposed combination of references fails to teach or suggest each and every element of the instant claims, Appellants submit that a *prima facie* case of obviousness has not been established and respectfully request reversal of the rejection.

Claims 7-9 are not unpatentable over Sambrook in view of Wang et al. '727 and Wang et al. '742 as evidenced by Pall Life Sciences and further in view of Waggoner (U.S. Patent No. 5,627,027) ("Waggoner").

Group 1: Claims 7-9

Claim 7 claims the method of Claim 1, wherein the cRNA is labeled. Claim 8 claims the method of claim 7, wherein the label is either radioactive or fluorescent. Claim 9 claims the method of claim 8, wherein the fluorescent label is a cyanine dye.

Each of Claims 7, 8 and 9 are ultimately dependent upon Claim 1. The application of the combined teachings of Sambrook, Wang et al. '727 and Wang et al. '742 to Claim 1 has been discussed previously herein. Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, the combined references fail to teach or suggest a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

The Examiner acknowledges that neither Sambrook nor Wang et al. 727 teach labeled RNA, and the Examiner provides no evidence or indication that Wang et al. '742

teaches or suggests labeled RNA. In an attempt to remedy this deficiency, the Examiner relies on Waggoner solely for an alleged teaching regarding the labeling of RNA using fluorescent cyanine dyes. As such, the addition of the Waggoner reference to the combination of Sambrook, Wang et al. '727 and Wang et al. '742 fails to cure the previously discussed deficiencies in the Sambrook - Wang et al. '727 - Wang et al. '742 combination, i.e., the combination of all four references fails to teach or suggest a cRNA purification method in which the method utilizes a membrane column wherein the membrane is not associated with an active binding agent or wherein the membrane passively retains a cRNA precipitate.

Since the proposed combination of references fails to teach or suggest each and every element of the instant claims, Appellants submit that a *prima facie* case of obviousness has not been established and respectfully request reversal of the rejection.

SUMMARY

I. Claims 3-6 are not indefinite under 35 U.S.C. § 112, second paragraph, because the rejection has been rendered moot in view of the Examiner's entry of the amendments proposed in the Amendment and Response filed May 25, 2007 which was responsive to the Final Office Action dated March 26, 2007.

II. Claims 1, 3-6, 10-15, and 20-21 are not obvious under 35 U.S.C. § 103(a) over Sambrook in view of Wang et al. '727, and further in view of the Wang et al. '742 as evidenced by Pall Life Sciences, because the combined references fail to teach or suggest a cRNA purification method as claimed.

III. Claims 7-9 are not obvious under 35 U.S.C. § 103(a) over Sambrook in view of Wang et al. '727 and Wang et al. '742 as evidenced by Pall Life Sciences and further in view of Waggoner, because the combined references fail to teach or suggest a cRNA purification method as claimed.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 3-6 under 35 U.S.C. § 112, second paragraph, and the rejection of Claims 1, 3-15, and 20-21 under 35 U.S.C. § 103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: September 14, 2007

By: _____
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CLAIMS APPENDIX

1. A method of preparing a cRNA sample substantially free of contaminants, comprising the following steps:

(a) preparing a cRNA sample;

(b) adding an organic solvent to said preparation of (a);

(c) contacting a cRNA isolation column with the organic preparation of step (b), wherein said cRNA isolation column comprises a membrane selected from the group consisting of polysulfone treated with hydroxypropylcellulose, PVDF (polyvinylidene fluoride), nylon, nitrocellulose, polysulfone, polysulfone and polyvinylpyrrolidone, PVP (polyvinylpyrrolidone), and composites thereof;

(d) adding to a preparation of step (c) one or more DNase enzymes;

(e) adding to a preparation of step (d) a wash buffer comprising a chaotropic salt; and

(f) eluting said cRNA in a purified form from said column of step (c).

3. The method of claim 1, wherein said membrane is a polysulfone and polyvinylpyrrolidone membrane.

4. The method of claim 3, wherein said polysulfone and polyvinylpyrrolidone membrane is an asymmetric membrane comprised of polysulfone and PVP.

5. The method of claim 3, wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 30 to about 40 μm on an upper side, and wherein said polysulfone and polyvinylpyrrolidone membrane has a pore size ranging from about 0.4 μm to about 0.6 μm on a lower side.

6. The method of claim 5, wherein said membrane has a pore size of about 0.4 μm on said lower side.

7. The method of claim 1, wherein said cRNA is labeled.

8. The method of claim 7, wherein said label is either radioactive or fluorescent.

9. The method of claim 8, wherein said fluorescent label is a cyanine dye.

10. The method of claim 1, wherein said purified cRNA is from about 55% to about 65% pure.

11. The method of claim 1, wherein said purified cRNA is from about 65% to about 75% pure.

12. The method of claim 1, wherein said purified cRNA is from about 75% to about 85% pure.

13. The method of claim 1, wherein said purified cRNA is from about 85% to about 95% or greater pure.

14. The method of claim 1, wherein said organic solvent is ethanol.

15. The method of claim 1, wherein said isolation column is either a SiCw column or an RNA isolation column.

20. The method of claim 1, wherein said one or more DNase enzymes is selected from the group consisting of DNase 1, DNase II, and a combination thereof.

21. The method of claim 1, wherein said chaotropic salt is selected from the group consisting of guanidine isothiocyanate, ammonium isothiocyanate, guanidine hydrochloride, and a combination thereof.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.